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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Penelope N. MARKHAM *et al.*

Serial No.: 09/816,761

Filed: March 23, 2001

For: BACTERICIDAL ANTIMICROBIAL METHODS AND COMPOSITIONS FOR USE IN TREATING GRAM POSITIVE INFECTIONS

Group Art Unit: 1645

Examiner: Elli Peselev

Atty. Dkt. No.: IFLX:003US/SLH

BRIEF ON APPEAL

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July 7, 2003
Date

Steven L. Highlander

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APPEAL BRIEF

BOX AF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant hereby submits an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Final Office Action dated December 5, 2002. This brief is due on July 7, 2003, by virtue of the Notice of Appeal received by the PTO on May 6, 2003 (July 6th being a Sunday). The fee for filing this Appeal Brief is attached hereto. Should any other fees be due, or the attached fee be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/IFLX:003US/SLH. Please date stamp and return the enclosed postcard to evidence receipt of this document.

I. Real Party in Interest

The real party in interest is the assignee, INFLUX Inc., Chicago, IL.

II. Related Appeals and Interferences

There are no interferences or appeals for related cases.

III. Status of the Claims

Claims 1-79 were filed with the original application. Claims 10, 11 and 61-77 have been canceled, and claims 41-43 are withdrawn consideration. Claims 1-9, 12 and 13 are allowed, and claims 14-40, 44-60 and 78-79 are rejected and are appealed. A copy of the withdrawn, allowed and rejected claims is attached as APPENDIX 1 to this brief.

IV. Status of Amendments

No amendments have been submitted following the final office action.

V. Summary of the Invention

The present invention provides antibiotic potentiators which are bactericidal in combination with a number of classes of antibacterial agents, and methods of use therefor. Specification at page 5, lines 2-4. In particular, the invention is drawn to combining an antibacterial agent, in the presence of a bacterium, with a potentiator selected from an acyl hydrazide and an oxy amide. Specification at page 5, lines 21-22.

VI. Issue on Appeal

Are claims 14-40, 44-60, 78 and 79 unpatenable as obvious under 35 U.S.C. §103 over Abbruzzeese *et al.* (U.S. Patent 4,058,613; Exhibit A) in combination with Pfaller *et al.* (*Antimcirobial Agents and Chemotherapy*, 1998; Exhibit B)?

VII. Grouping of the Claims

The claims do not stand and fall together, as discussed in §IX.C, below.

VIII. Summary of the Argument

The examiner has combined two references – Abbruzzese and Pfaller – for no better reason than that they both deal with antibiotics, clearly relying on improper hindsight to do so. Notably, there is no suggestion in either document of combinations therapies. The examiner offers no rebuttal – factual or legal – and simply reiterates the conclusion of obviousness. This failure alone mandates reversal of the rejection.

The examiner has also glossed over the complexities of drug combinations in arguing likelihood of success. Again, no evidence is offered to establish that one of skill in the art would, in fact, find such combinations to predictably give the desired results. In point of fact, the examiner simply uses hindsight again, this time for establishing likelihood of success. For a second reason, the rejection should be found improper.

Finally, the examiner has failed to address the fact that numerous claims do not recite the 8-hydroxy quinoline of the Abbruzzese reference. This means that for these claims, there is no primary reference that teaches the limitations of the claims. Clearly, separate issues of patentability are presented by this fact situation, and these claims exhibit further grounds upon which their patentability is argued and not rebutted.

IX. Argument

Claims 14-40 and 44-60, 78 and 79 stand rejected under §103 as obvious over Abbruzzese and Pfaller. According to the examiner, Abbruzzese teaches that 8-hydroxy quinoline has *in vitro* antibacterial activity, and thus, it would be obvious to combine this

compound with any other antibiotic, such as those disclosed by Pfaller. Applicants submit that this rationale cannot support a proper obviousness rejection.

Any obviousness rejection requires that the prior art provide (a) enabling technology for each claimed element, (b) motivation to combine references, as well as (c) a likelihood of success. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1987). Without ***all*** of these elements, no obviousness rejection can stand. Applicants submit that the present rejection fails for at least two of these reasons, namely, that (i) the prior art is silent as to a motivation to combine any one of the three claimed potentiators – an acyl hydrazide, an oxy amide or an 8-hydroxy quinoline – with an antibiotic, and (ii) that even if combined, there would be no ***reasonable*** predictability with regard to the outcome of the combination.

A. Motivation to Combine

First and foremost, the examiner has not made out a *prima facie* case that one of skill in the art, looking at the cited references, would be motivated to combine 8-hydroxy quinoline (much less an an acyl hydrazide or an oxy amide) with a secondary agent. The examiner has pointed to no particular teaching in Abbruzzese that would instruct the skilled artisan to make such a combination with a second antibiotic agent. Similarly, the examiner has not indicated that Pfaller provides anything but a laundry list of individual antibiotics.

Thus, applicants submit that there is no showing on the record of a ***clear and definitive suggestion in the cited art that one should make the claimed combination***. Put another way, there are literally millions of potential drug combinations, and the present record is grossly deficient to establish that this particular type of combination should be made.

In re Jones, 21 USPQ2d 1941 (Fed. Cir. 1992) is particularly instructive in this situation. This case dealt with the obviousness of a novel salt of the acid known as dicamba. The PTO

alleged that prior art, which disclosed a genus encompassing the salt, rendered a claim to that compound obvious. There, the court found the record lacking with regard to motivation when selecting from such a large number of possibilities:

> Conspicuously missing from this record is any ***evidence***, other than the PTO's speculation (if it can be called evidence) that one of skill in the herbicidal art would have been motivated to make the modifications [to] the prior art salts necessary to arrive at the claimed ... salt."

Jones at 1944 (emphasis in original). The court went on to cite *In re Lalu*, 223 USPQ 1257 (Fed. Cir.) for the same proposition. "The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound." *Lalu* at 1258.

Thus, the prior art, not the examiner, must provide motivation for this particular species of combination. Here, the record shows no evidence, beyond the mere allegation that antibiotic combinations are known, that would lead one to use the selected potentiators with an antiobiotic. As such, appellants submit that this rejection also suffers from the same defect as described in *Jones* – lack of motivation – and a *prima facie* case can therefore not stand.

In rebuttal, the examiner has offered not one single word. Rather, the final Office Action simply acknowledges that the prior art must provide the motivation to combine the references, then merely concludes that the combination would have been obvious "because [a person having ordinary skill in the art] would have expected [the] resulting combination to possess antibacterial properties." That statement, unfortunately, addresses a different issue – likelihood of success. Thus, on the record, the examiner has failed entirely to find motivation in the prior art to combine the cited references. As such, appellants maintain their position that the rejection is defective.

B. Likelihood of Success

In the previous response, appellants argued that despite the examiner's oversimplification of the issues, it is far from straightforward to predict which drugs should be combined as part of a therapeutic program. To the contrary, scientists have repeatedly established that drug combinations ***are not*** uniformly combinable. Pharmaceutical companies around the world spend ***millions*** of dollars conducting screening assays for suitable drug combinations. In fact, before any combination therapy can be approved for use on humans (or even approved for testing in humans) by the appropriate regulatory authority, it must be shown to be efficacious and safe to use in humans in the relevant animal model/cell culture testing. Certainly, until such testing is completed, no one with approval authority is willing to predict the ultimate usefulness of any given drug combination.

While the combinations that ***do*** turn out to work (*i.e.*, are effective and non-toxic) may seem logical in retrospect, a proper obviousness analysis also requires consideration of the other combinations which fail, of which there are many. It is only through a hindsight analysis, which the examiner applies here, that one can find the prior art to have suggested both the combination, ***and*** predicted its likely success. *In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. Sup. Ct. 1965). As such, the rejection is improper for this second reason, even assuming that a proper combination of the references cited by the examiner could be advanced (which it cannot).

As discussed above, the examiner clings to the bare statement that "[a person having ordinary skill in the art] would have expected [the] resulting combination to possess antibacterial properties." The question, of course, is ***why***? Is there any evidence of record to suggest that

these particular compounds would work well together? Would work at all together? Would not be toxic? In fact, there is ***no*** such evidence of record, rendering the rejection void. See *In re Ahlert*, 165 USPQ 421 (CCPA 1970) ("Assertions of technical facts in areas of esoteric technology must always be supported by citation to some reference work recognized as standard in the pertinent art .... Allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported ....").

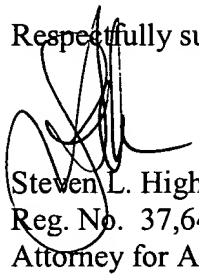
C. Separate Patentability

The examiner has rejected all pending claims as obvious over the cited references. However, appellants point out that no reference has been cited that implicates acyl hydrazides or oxy amides, alone or in a combination therapy. Therefore, the examiner has improperly rejected many of the dependent claims which do not recite 8-hydroxy quinoline, for example, claims 15-22, 29-36, or 45-52, which exhibit separate issues of patentability with respect to the claims that encompass 8-hydroxy quinoline. As such, a *prima facie* case has not been made out against these claims for this additional reason.

X. Conclusion

It is respectfully submitted, in light of the above, that all claims are non-obvious over the cited art. Therefore, appellants request that the Board overturn each of the pending grounds for rejection.

Respectfully submitted,



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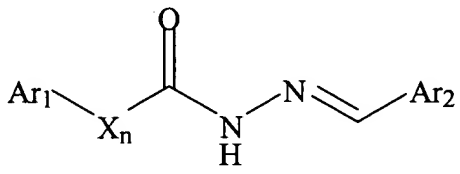
512-536-3184

Date: July 7, 2003

APPENDIX 1 -- PENDING CLAIMS

1. A method for increasing the sensitivity of a bacterium to an antibacterial agent comprising contacting the bacterium with an antibiotic potentiator, wherein said potentiator is an acyl hydrazide or an oxy amide.

2. The method of claim 1, wherein said acyl hydrazide has the general formula:



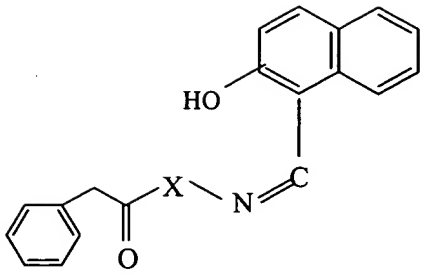
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

3. The method of claim 2, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

4. The method of claim 2, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

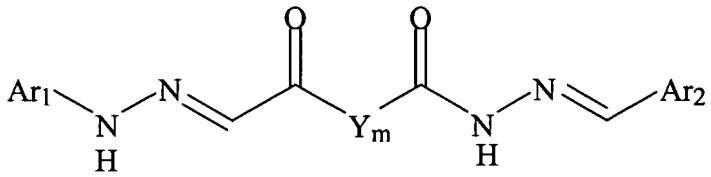
5. The method of claim 1, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

6. The method of claim 1, wherein said acyl hydrazide has the formula:

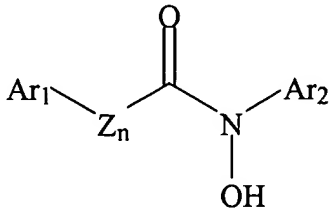


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

7. The method of claim 6, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

8. The method of claim 1, wherein said oxy amide has the formula:



(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

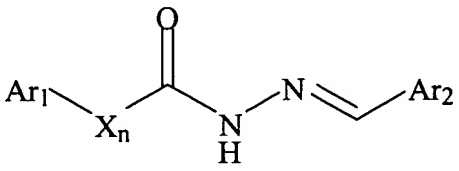
9. The method of claim 8, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

12. The method of claim 1, wherein said bacterium is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

13. The method of claim 1, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

14. A method of treating a subject with a bacterial infection comprising administering to said subject an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

15. The method of claim 14, wherein said acyl hydrazide has the general formula:



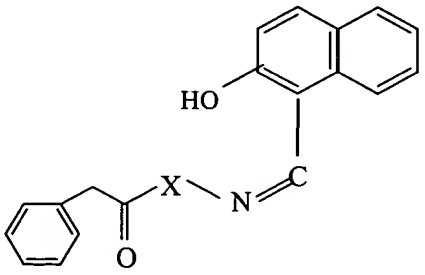
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

16. The method of claim 15, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

17. The method of claim 15, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

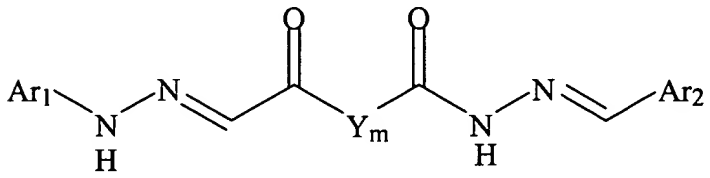
18. The method of claim 14, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

19. The method of claim 14, wherein said acyl hydrazide has the formula:

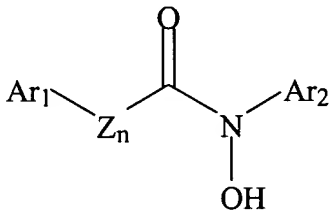


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

20. The method of claim 19, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

21. The method of claim 14, wherein said oxy amide has the formula:

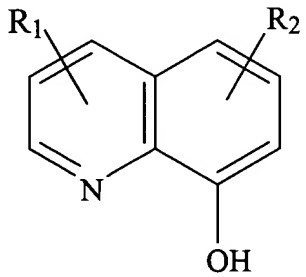


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

22. The method of claim 21, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

23. The method of claim 14, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

24. The method of claim 23, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

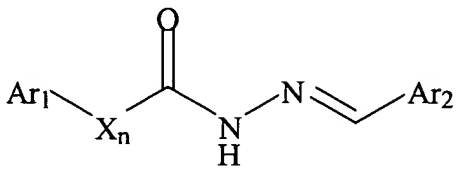
25. The method of claim 14, wherein said bacterial infection is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

26. The method of claim 14, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

27. The method of claim 26, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

28. A bactericidal pharmaceutical composition comprising an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

29. The composition of claim 28, wherein said acyl hydrazide has the general formula:



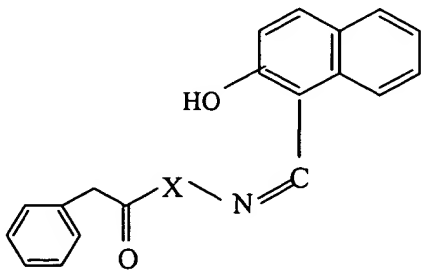
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

30. The composition of claim 29, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

31. The composition of claim 29, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

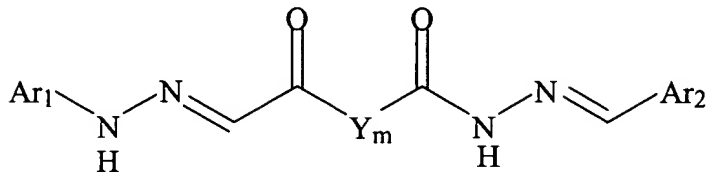
32. The composition of claim 28, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

33. The composition of claim 28, wherein said acyl hydrazide has the formula:

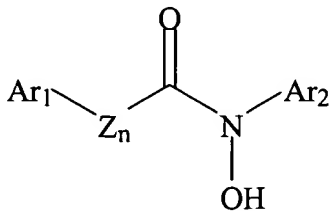


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

34. The composition of claim 33, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

35. The composition of claim 28, wherein said oxy amide has the formula:

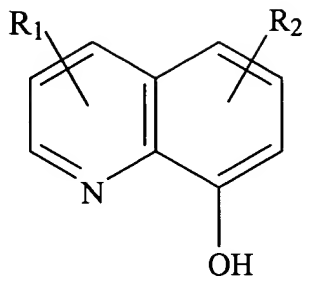


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

36. The composition of claim 35, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

37. The composition of claim 28, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

38. The composition of claim 37, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

39. The bactericidal composition of claim 28, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

40. The bactericidal composition of claim 39, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

41. A method of screening for candidate acyl hydrazide antibiotic potentiators, oxy amide antibiotic potentiators or 8-hydroxy quinoline potentiators comprising:

(a) contacting a bacterial cell with an antibacterial agent;

(b) contacting a bacterial cell with said antibacterial agent and an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline; and

(c) comparing the bactericidal effect of said antibacterial agent in the presence and absence of said acyl hydrazide, oxy amide or 8-hydroxy quinoline,

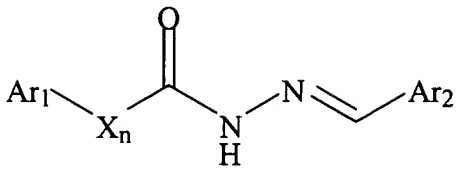
wherein a decrease in bacterial cell viability indicates said candidate acyl hydrazide, oxy amide or 8-hydroxy quinoline is an antibiotic potentiator.

42. The method of claim 41, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

43. The method of claim 41, wherein said bacterial cell is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

44. A method of treating a subject for a bacterial biofilm infection comprising administering to said subject an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

45. The method of claim 44, wherein said acyl hydrazide has the general formula:



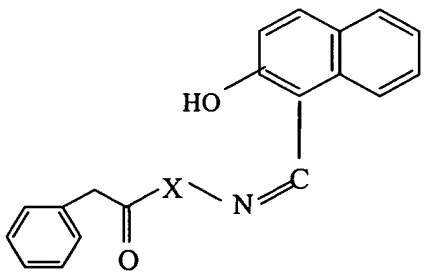
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

46. The method of claim 45, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

47. The method of claim 45, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

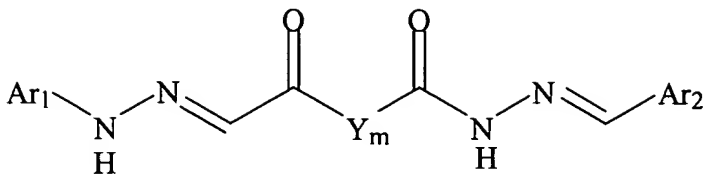
48. The method of claim 44, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

49. The method of claim 44, wherein said acyl hydrazide has the formula:

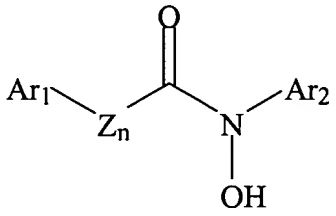


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

50. The method of claim 49, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

51. The method of claim 44, wherein said oxy amide has the formula:

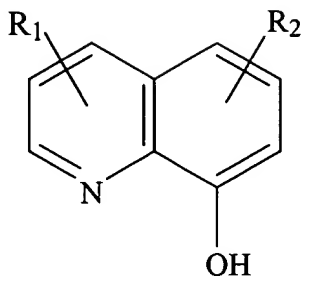


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

52. The method of claim 51, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

53. The method of claim 44, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

54. The method of claim 53, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

55. The method of claim 44, wherein said biofilm is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

56. The method of claim 52, wherein said infection is resistant to antibacterial agents.

57. The method of claim 56, wherein said infection is a chronic infection or persistent infection.

58. The method of claim 54, wherein said infection is endocarditis, osteomyelitis, an infection in a neutropenic subject or a biomaterial infection.

59. The method of claim 44, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides,

oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

60. The method of claim 59, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

78. A method for increasing the bactericidal action of an antibacterial agent comprising:

(a) contacting a bacterial cell with an antibacterial agent; and

(b) contacting said bacterial cell with an acyl hydrazide potentiator, an oxy amide potentiator, or an 8-hydroxy quinoline potentiator,

wherein said potentiator promotes the intracellular accumulation of a metal.

79. The method of claim 78, wherein said metal is iron, copper or manganese.

APPENDIX 2 -- EXHIBITS